Papers and Originals

Osteomalacia with Long-term Anticonvulsant Therapy in Epilepsy

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Summary: The investigation and treatment of osteomalacia are described in four patients with epilepsy treated with long-term anticonvulsant therapy. It is suggested that drug-mediated enzyme induction may be the mechanism responsible by causing a greatly increased inactivation of vitamin D in these patients.

Introduction

Biochemical abnormalities suggestive of osteomalacia have been described in a group of patients resident in an epileptic colony and consuming a diet containing adequate amounts of vitamin D (Richens and Rowe, 1970). Similar findings have been described by other workers (Kruse, 1968, reported by Reynolds, 1970). This paper describes the detailed investigation and response to treatment of two patients with epilepsy and osteomalacia who had been receiving long-term anticonvulsant therapy. Two further patients with similar pathology are more briefly described. The possible causes of this association are discussed.

Case 1

At the age of 5 months a 16-year-old boy had developed increasingly frequent clonic spasms. At the age of 2 years these spasms were replaced by flickering of the face and different parts of the body. Grand-mal seizures developed at the age of 10 and have persisted ever since, occurring up to six times daily. He had never been in status epilepticus. He also suffered from frequent petit-mal attacks. There was no other relevant past or family history.

At University College Hospital in June 1967 his I.Q. was 65-67 (Terman-Merrill scale). The electroencephalogram was multifocal, with gross abnormalities which were greater in the left frontal leads. Radiology showed a small calcified lesion deep in the left frontoparietal area. The cerebrospinal fluid, lumbar air encephalogram, and a left carotid angiogram were normal. No definitive diagnosis of the intracerebral lesion was possible. His plasma calcium was 8.7-9.1 mg./100ml. (corrected for plasma specific gravity), phosphorus 5.1 mg./100 ml., alkaline phosphatase 16.5 King-Armstrong units, and chemistry was otherwise normal. His clinical condition was not altered by phenytoin, primidone, ethosuximide, and amphetamines, but it appeared to be worsened by barbiturates.

He entered an epileptic colony in September 1969, when he was found to be suffering from phenytoin overdosage, with ataxia, diplopia, and nystagmus; this responded to halving his phenytoin from 300 to 150 mg. daily. Folate deficiency was discovered and he was given oral folic acid therapy. He was admitted to the metabolic ward, University College Hospital, in January 1970 after a survey at the epileptic colony had shown that his plasma chemistry was suggestive of osteomalacia. He was having several fits daily. On examination he was a normally adolescent boy with obvious mental retardation, slow slurred speech, and sluggish co-ordination. His height and weight were on the 10th percentile. He

had gingival hypertrophy. The left plantar reflex showed an extensor response, but there was no other abnormality.

Anticonvulsant therapy had been continuous since 1954, from the age of 5 months, and he had received almost every possible drug combination. He had been taking phenytoin 150-300 mg. daily almost continuously since long before June 1967; during most, but not all, of the period since June 1967 he was also taking primidone 250 mg. three times a day, but he had received barbiturates for only a few months. Throughout his admission he continued to receive primidone 250 mg. t.d.s., phenytoin 50 mg. t.d.s., chlorthalidone 5 mg. t.d.s., and folic acid 5 mg. daily.

Relevant investigations on admission are shown in the Table. Investigations which gave entirely normal results included full blood count, red cell indices, plasma folate and vitamin B₁₂, urea and other electrolytes, cortisol levels, and serum proteins. The ultrafilterable calcium was 4.2 mg./100 ml. An electrocardiogram showed hypocalcaemic changes. Histochemical studies of his jejunal biopsy (Professor I. M. P. Dawson) were also normal apart from aminopeptidase in the glands, a finding somewhat suggestive of regenerating epithelium (? an aftermath of previous folate deficiency). A bone biopsy showed osteomalacia (Fig. 1). Phosphate infusion studies (Stamp and Stacey, 1970) showed a theoretical renal phosphorus threshold of 4.4 mg./100 ml., glomerular filtration rate 114 ml./min., and TmP 6.2 mg./min/1.73 m.² Radiology of skull showed calcification deep in the left frontal lobe; the vertebrae showed Schmorl's nodes, but the skeleton was otherwise normal on x-ray examination.

Treatment was begun with vitamin D₂ by intravenous injection, 50 µg. daily for 16 days, followed on the 17th day by the first of three injections of 350 µg. given intravenously at weekly intervals. Twenty-six days after beginning vitamin D₂ he was given whole-body ultraviolet irradiation to the limit of tolerance (three times weekly) for 41 days. He was begun on caps. vit. A and D (B.P.C.) 4 daily (1,800 i.u. of vitamin D daily) eight days before discharge. Changes in plasma calcium, phosphorus, and alkaline phosphatase throughout treatment are shown in Fig. 2. Thirty-five days after beginning ultraviolet therapy his theoretical renal phosphorus threshold had risen to 5.5 mg./100 ml. (normal intra-individual S.D. ±0.28 mg./100 ml.). A repeat iliac crest biopsy after ultraviolet therapy showed entirely normal coverage with osteoid (Fig. 3). Urine calcium excretion did not alter notably during his admission

FIG. 1.—Case 1. Iliac crest biopsy. Undecalcified section. There is extensive coverage of the bone surfaces by moderately thick osteoid seams. A few inert and resorbing surfaces are present. (Solochrome cyanin. × 40.) The surface counts showed osteoid 53%, resorption 13%, inert 34%.

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Summary of Initial Investigations on Three of the Four Patients with Epilepsy and Osteomalacia on Long-term Anticonvulsant Therapy

Case No.	Plasma						Urine			Faecal Fat (g./day)	Jejunal Histology	Bone Histology		
	Ca	P	Alkaline Phosphatase (K.A.U.) Acrylamide Gel Electrophoresis		Mg (mg./100ml.)	HCO ₃ (mmole/l.)	Oral Glucose Tolerance (mg./100 ml.)		Ca (mg./24 hours)				Amino-acid Chromatogram	D-xylose Excretion (g./5 hours after 15 g. oral load)
	(mg./100 ml.)						Fasting	Max.						
1	7.3 (S. G. 1028)	3.5	27	90% bone	2.17	20-23	60	155	56	Normal	4.2	4.1	Normal	Pronounced* osteomalacia
2	8.3 (S. G. 1024)	2.0	23	90% bone		Normal	70	160	171	Low mol. wt. Amino-aciduria Normal	1.5	2.7	—	Pronounced osteomalacia
3	8.4†		21-27†								2.3	3.6-4.4	Normal	—

* Fig. 1.

† Initial investigations elsewhere before treatment.

and the frequency of his fits remained unchanged. Since his discharge he has received treatment with oral vitamin D₃ 1,800 i.u. daily and plasma levels of calcium, phosphorus, and alkaline phosphatase have remained in the normal range.

Case 2

A 61-year-old woman was admitted to the metabolic ward in May 1970 with a 21-month history of back pain and progressive muscular weakness. She first developed major epilepsy at the age of 18. She had for many years been suffering only occasional transient losses of consciousness preceded by an aura. She had had continuous anticonvulsant therapy since the age of 21. For most of the last 23 years this had consisted of phenytoin 100 mg. t.d.s. and primidone 250 mg. t.d.s., both of which she was receiving on admission. In 1965 she suffered a simple Colles's fracture, which took over three months for complete radiological healing. Twenty-one months before admission she had had a sudden attack of back pain in the dorsal region while in bed, and recurrent scapular pains had since persisted. Working as a cleaner she had gradually developed progressive difficulty in lifting buckets or rising from sitting and squatting positions, and also had difficulty in turning over in bed at night. She complained of exertional dyspnoea. There were no bowel or urinary symptoms. There was no relevant known childhood or family history.

FIG. 2—Case 1. Changes in plasma calcium, phosphorus, and alkaline phosphatase during treatment of osteomalacia with parenteral vitamin D₂ (350 µg. weekly) and ultraviolet irradiation.

On examination she appeared rather frail, but there were no abnormal findings outside her musculoskeletal system. Skeletal measurements were: crown to pubis 76 cm., pubis to sole 81 cm., span 160 cm.—findings which suggested some 4-5 cm. of trunk shortening. There was slight weakness of trunk flexion, and slight but definite weakness of hip flexion, extension, and abduction. Relevant investigations on admission are shown in the Table. Other results, as in Case 1, were normal. Radiology showed irregular vertebral collapse with minimal biconcavity of the vertebrae (Fig. 4); there were two old rib fractures and some pelvic asymmetry. The results of electromyography were consistent with early myopathy.

The patient was further investigated under full metabolic balance conditions. Initial calcium balance was virtually zero. She was first treated with two weekly doses of vitamin D₂ 350 µg. by intravenous injection. No significant changes occurred either in plasma chemistry or in calcium balances, except for a minimally positive shift in her calcium balance at the end of this period. Her myopathy, however, resolved within a few days. She was then given whole-body ultraviolet irradiation to the limit of tolerance (three times weekly). Calcium balance became increasingly positive. Plasma phosphorus rose strikingly after a delay. A minor rise in plasma calcium and a slow fall in alkaline phosphatase levels occurred by the end of her admission. These changes are shown in Fig. 5.

Case 3

A 31-year-old woman was admitted for investigation in May 1969. Previous investigation and treatment had already been carried out elsewhere and these earlier findings are reported here. The patient developed permanent epilepsy and mental retardation from the age of 2, following an attack of meningitis. She had been treated almost continuously since then, first with phenobarbitone and primidone, and from 1966 with primidone 250 mg. four times a day and phenytoin 100 mg. three times a day. Epilepsy was never fully controlled but she remained well, within her own limits, until March 1968, when she developed difficulty in walking and climbing stairs. Her gait became bizarre and bilateral hip fractures (trochanteric and subcapital) were discovered. During the first surgical correction her bones were found to be very soft.

FIG. 3—Case 1. Iliac crest biopsy. Undecalcified section. There are only a few narrow osteoid seams present. The remaining surfaces are inert or undergoing resorption. (Solochrome cyanin. $\times 40$.) The surface counts now showed osteoid 11%, resorption 11%, inert 78%.

FIG. 4.—Case 2. Lateral spine on June 1970. The vertebral bodies are not particularly osteoporotic but a mid-thoracic body is compressed and a lower thoracic one wedged and with a Schmorl's node on the upper surface. These are healed and presumably took place during a convulsion some years previously.

Subsequent investigations are shown in the Table. She was then treated with vitamin D 75,000 units daily and calcium supplements, but was referred on account of her very slow progress. She had a history of occasional bouts of diarrhoea and her parents emphasized her fastidious eating habits. There was no relevant family history.

On examination she was still in a right hip spica. Intelligence was low. Motor power was very difficult to determine owing to immobilization and pain in the left hip. All routine laboratory investigations were normal throughout; thus the plasma calcium was 9.1 mg./100 ml. (S.G. 1021-2), phosphorus 3.6 mg./100 ml., and alkaline phosphatase 7 King-Armstrong units. Radiology showed generalized thinning of cortical bone and multiple, mostly healed, rib fractures which strongly supported the diagnosis of healing osteomalacia.

On discharge it was written: "There was absolutely no doubt that she has had osteomalacia. . . . The remaining likely retrospective diagnosis is nutritional osteomalacia." Since then she has made progress gradually in calipers. The right hip fracture has never united though the left hip has healed.

Case 4

A 58-year-old housewife was referred in May 1966 with a history of increasing bone pains, pathological long-bone fractures, and a previous megaloblastic anaemia responding to folic acid. Investigations showed the presence of mild malabsorption. Intestinal biopsy showed partial villous atrophy. The 24-hour faecal fat was 6.8 g., falling to 3.4 g. on a gluten-free diet. We were puzzled by the relative severity of her bone disease, and especially on follow-up in noting the rather slow response of her osteomalacia clinically and biochemically on continuing the gluten-free diet and the supplementary doses of vitamin D₂. We were persuaded that she was keeping scrupulously to the diet. Even more puzzling was the return of symptoms and rise in plasma alkaline phosphatase during 1968 and early 1969, requiring further loading with vitamin D₂ (Fig. 6).

Discussion

Many toxic or hypersensitivity reactions produced by anticonvulsant drugs are now well known (reviewed by Reynolds, 1970). The apparent association between long-term anticonvulsant therapy (particularly phenytoin and primidone) and a defect in calcium and phosphorus metabolism was first reported by Kruse (1968) in children and adolescents. Since then Richens and Rowe (1970) have found a significantly increased incidence of hypocalcaemia and raised alkaline phosphatase levels among patients of all ages on long-term anticonvulsant therapy. Abnormal plasma levels of calcium and alkaline phosphatase were corrected by vitamin D therapy in those patients who received it.

The present study describes in more detail the finding of osteomalacia in four epileptic patients receiving long-term therapy. In one of them (Case 1) treatment was carefully monitored until final cure of bone disease; thus abnormal plasma levels of calcium, phosphorus, and alkaline phosphatase were corrected, the theoretical renal phosphorus threshold rose by an extent which was probably significant (Stamp and Stacey, 1970), and histological cure of osteomalacia was confirmed on bone biopsy. Cure of osteomalacia in Case 1 and rapid healing in Case 2 were accomplished by a combination of ultraviolet irradiation and parenteral vitamin D therapy in a dose (50 µg. daily) too small to affect any of the known metabolic forms of the disease apart from specific malabsorption of vitamin D in liver disease (Dent and Stamp, 1970). Full evaluation of the relative effects of vitamin D administration and of ultraviolet irradiation in these two patients was not possible. The effect of ultraviolet therapy, however, may have been greater than the effect of calciferol, and the rise in plasma phosphorus levels to supranormal values was particularly striking.

A common mechanism is likely for the production of osteomalacia by the major anticonvulsant drugs phenytoin, primidone, and phenobarbitone, in view of their obvious similarities, not only in structure but also in both therapeutic and toxic effects (reviewed by Toman, 1965). In the past few years a wide range of drugs has been found active in promoting hepatic enzyme induction (reviewed by Kuntzman, 1969).

FIG. 5.—Case 2. Changes in plasma calcium, phosphorus, alkaline phosphatase, and calcium balance during treatment of osteomalacia with parenteral vitamin D₂ (350 µg. weekly) and ultraviolet irradiation.

FIG. 6.—Case 4. Long-term follow-up of alkaline phosphatase levels. This patient had osteomalacia with minimal steatorrhoea, partial villous atrophy, and a slow response to gluten-free diet, which recurred on stopping therapy with vitamin D₂, due to the primidone she was being given.

Phenobarbitone and phenytoin exert a definite and almost universal effect on steroid metabolism. Thus the hormonal activity of a wide range of administered steroids, including cortisol, androgens, and oestrogens, is decreased and the excretion of their more polar inactive derivatives following enhanced reduction or hydroxylation, or both, is promoted (Kuntzman, 1969). Similar hydroxylation reactions are prominent in many of the mechanisms of drug detoxication.

The metabolism of the antirachitic sterols requires much further clarification. The liver, however, appears to be the main organ responsible for the conversion of cholecalciferol (vitamin D₃) to 25-hydroxycholecalciferol (Ponchon and DeLuca, 1969), the probable metabolically active form of vitamin D (DeLuca, 1969a). The route by which these steroids are further metabolized to inactive excretory products is still unknown, but probably this occurs by further hydroxylation or reduction, or both, to more polar metabolites (DeLuca, 1967)—as occurs in the normal metabolism of adrenocortical hormones. Conjugation of vitamin D to form more soluble glucuronides also occurs during normal metabolism (Avioli, 1969), while bilirubin conjugation is appreciably enhanced by anticonvulsant drugs. There is thus strong circumstantial evidence at least that osteomalacia during anticonvulsant therapy may be caused by a mechanism of enzyme induction leading to increased breakdown of vitamin D to inactive products. Continuous anticonvulsant administration could thus increase significantly the daily vitamin D requirement. Moreover, one of us (D.J.F.R.) has shown that the hypercalcaemia and renal calcification produced by vitamin D intoxication in rats may be strikingly lowered by the simultaneous oral administration of phenobarbitone (private communication).

Case 4 is of interest in that only one dose of one antiepileptic drug had been given throughout the course of the disease and its treatment. Since her alkaline phosphatase level was never lowered to normal (<10 King-Armstrong units) the dose of 1.25 mg. of vitamin D₂ was probably never fully effective. This is 100 times the normal adult requirement of the vitamin. Probably the behaviour on the gluten-free diet was largely due to primidone-induced osteomalacia, and the previous severe osteodystrophy was due

to the combined effect of the primidone and the malabsorption.

A specific malabsorption defect located in the intestinal mucous membrane can also not be excluded. Three of our four patients (Cases 1–3) had no evidence of intestinal abnormality, apart from defective D-xylose absorption, a finding which has been reported during phenytoin therapy (Reynolds et al., 1965). Nevertheless, possibly this therapy may cause a specific derangement of the mucosal vitamin-D-mediated calcium-transport system (reviewed by DeLuca 1969b).

Certain further considerations arise from the present study. Firstly, the development of hypocalcaemia during treatment of epilepsy may theoretically tend to worsen the frequency of seizures. Hence possibly plasma calcium levels should be monitored, at least in those patients receiving high doses of several drugs. Secondly, bone radiology is not adequate to exclude the presence of metabolic bone disease. We have seen florid rickets in two children on long-term anticonvulsants; however, in some patients the bones may appear normal, while in others more complex changes may be found—for instance, in Fig. 2 of Kruse (1968) the appearances of metaphysical rarefaction were similar to those seen in severe cases of idiopathic juvenile osteoporosis (Dent, 1969). Our Cases 1, 2, and 4 also showed changes of osteoporosis. An association between epilepsy and osteoporosis has been strongly suspected for some years (Dent and Watson, 1966), though without consideration of the possible effects of therapy. Such an association might be more apparent than real, however, since epileptic injuries might reveal latent mild osteoporosis.

Finally, this long delay in recognizing the association between osteomalacia and universally used anticonvulsant therapy deserves comment. The third and fourth cases reported here have been diagnosed only in retrospect. The often indefinite symptomatology of osteomalacia, with its vague bone pains and muscle weakness, is always in danger of being overlooked. This danger must be increased in patients who suffer from mental and physical slowness, which in severe epilepsy may be the result not only of the disease but also of its therapy.

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